Chapter

Polyphenols of *Salvia miltiorrhiza* in Aging-Associated Cardiovascular Diseases and Cancer

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Abstract

With the increasing lifespan of human, cardiovascular diseases (CVDs) and cancer are the main diseases leading to the death in the world. Aging is related to a progressive decline in cardiovascular function and structure. While human body suffer from oxidative stress, reactive oxygen species (ROS) are generated as metabolic by-products, which lead to inactivate proteins, damage nucleic acids, and alter the fatty acids of lipids. The accumulation of this oxidative damage contributes to the development of heart disease, diabetes, chronic inflammatory diseases, and cancer. Polyphenols have been widely studied as an anti-oxidant agent in the world. Danshen, the dried root or rhizome of *Salvia miltiorrhiza* Bunge. is a common Traditional Chinese medicine used in cardiovascular disease and cancer. The main polyphenols in Danshen are phenolic acids (including Salvianolic acids A and B, rosmarinic acid, and their derivatives) and flavonoids. Salvianolic acids have potent anti-oxidative capabilities due to their polyphenolic structure and exhibit cardiovascular protection through mechanisms of ROS scavengers, reduction of leukocyte-endothelial adherence, inhibition of inflammation and indirect regulation of immune function. Salvianolic acids A and B have been reported to owe anti-cancer, anti-inflammatory activities not only through inducing apoptosis, halting cell cycle and adjourning metastasis by targeting multiple deregulated signaling networks of cancer but also sensitizing cancer cells to chemotherapeutic agents.

Keywords: *Salvia miltiorrhiza*, polyphenol, Traditional Chinese medicine, cardiovascular disease, cancer

1. Introduction

With the increasing lifespan of human, cardiovascular diseases (CVDs) and cancer are the main diseases leading to the death in the world [1]. Aging is related to a progressive decline in cardiovascular function and structure. The major CVDs include ischemic heart disease, cardiomyopathy, hypertensive heart disease, atrial fibrillation, stroke, aortic aneurysm, rheumatic heart disease, endocarditis, and peripheral arterial disease [2].

There are many oxidants surrounding our environment even persisted inside the human body. While human body suffer from oxidative stress, reactive oxygen

species (ROS) are produced from the respiratory chain and leading the electron transfer. Superoxide radical ($O_2^{\bullet-}$) which dismutates from hydrogen peroxide (H_2O_2) and molecular oxygen (O_2) is a toxic compound after the ROS stimulation [3, 4]. ROS are related to inactivate proteins, damage nucleic acids, and alter the fatty acids of lipids. When those oxidative intracellular components in turn to perturbations in membrane structure and function, those reaction might lead to cell damage. The accumulation of this oxidative damage for a long period of time will leading the development of heart disease, diabetes, chronic inflammatory diseases, cancer, and several neurodegenerative diseases in the aging process.

Polyphenols have been widely studied as an anti-oxidant agent in the world. They are common nutrient antioxidants, mainly derived from fruits, vegetables, tea, coffee, cocoa, mushrooms, beverages, and Traditional Chinese medicine [5, 6]. Traditional Chinese medicine (TCM) are widely used for a long time in Asia countries. Most TCM source come from plants, including leaf, stem, roots or whole plants. Polyphenols are content rich in plants, and so are TCM. Danshen, the dried root or rhizome of *Salvia miltiorrhiza* Bunge. is a common TCM used in cardiovascular disease and cancer [7–9]. Following, we will make a discussion of aging-associated CVDs, cancer and *Salvia miltiorrhiza* (Danshen).

2. The monographs of aging-associated cardiovascular disease, cancer and *Salvia miltiorrhiza*

2.1 Aging-associated cardiovascular disease

The epidemic of CVDs has taken on a global dimension. CVDs now represent more than 30% of all deaths worldwide. According to the World Health Report, CVDs were responsible for 15 million annual deaths worldwide. Especially in developing countries, 9 million deaths every year while 2 million deaths in economies in transition [10].

CVD is positive related to human's age. By 2030, approximately 20% of the population will be aged 65 or older. At that time, the prevalence of CVD will exponential increase due to the fact that additional 27 million people will have hypertension, 8 million coronary heart disease, 4 million stroke and 3 million heart failure [11]. In this age group, CVDs will result in 40% of all deaths and rank as the leading cause and cost triple payment for treatment [12, 13].

Consistently, researchers have found that many of the factors underlying age-related changes in the arteries are also implicated in the development of CVD [14]. The incidence and prevalence of common CVDs such as hypertension, atherosclerosis, coronary and cerebral artery disease are increasing at about age 45 in men and age 55 in women [15]. These diseases may develop to increase in the prevalence of congestive heart failure and stroke during aging.

Aging is accompanied by changes in vascular structure and function, especially in the large arteries [16]. The aging cardiovascular tissues are exemplified by pathological alterations including hypertrophy, altered left ventricular (LV) diastolic function, and diminished LV systolic reverse capacity [17], increased arterial stiffness, and impaired endothelial function.

Endothelial dysfunction [18] is one of the major pathologic change of CVDs, besides, increasing intima media thickness, vascular stiffness [19], vesicular smooth muscle cells hypertrophy and proliferation and increasing vessel diameter are related to aging vessels. Impaired endothelial vasodilation is an early sign of arterial aging before the clinical manifestations of vascular dysfunction [20]. As endothelial cells age, they exhibit a reduction in endothelial nitric oxide synthetase (eNOS)

activity, reducing the abundance of nitric oxide (NO) [21]. NO is a vasodilator produced by endothelial cells, and related to regulate vascular tone, inhibiting vascular inflammation, thrombotic events, and aberrant cellular proliferation [22].

Aging has also a remarkable effect on the heart [23]. The number of cardiac myocytes lessen while heart weight gains with age. The functional cardiac cell continued loss come with the lower regenerative activity from 1% to 0.4% per year of age 20 to 75 years [24]. Most of researches found no obvious difference between male and female in increasing atrial volume [25] and cardiac fibrosis [26]. Although one study of cardiac extracellular matrix proteins found that senior women had a greater amount of collagen and other extracellular matrix proteins in the LV than senior men [27]. A recent work has clearly demonstrated that age-dependent mitochondrial DNA damage is an important substrate underpinning the pathophysiology of cardiac arrhythmias [28]. Another important pathological feature associated with aging is the calcification of aortic and mitral valves which triggers stenosis/insufficiency resulting in cardiac pressure/volume overload [29].

2.2 Cancer

Cancer is the second leading cause of death globally after ischemic heart disease, accounting for an estimated 9.6 million deaths, or one in six deaths, in 2018 and accounting for nearly 10 million deaths in 2020, but will likely become the first for nearly 18.63 million deaths in 2060 [30, 31]. Lung, prostate, colorectal, stomach and liver cancer are the most common types of cancer in men, while breast, colorectal, lung, cervical and thyroid cancer are the most common among women. It might prevent about one-third to half of cancer death after modifying or avoiding key risk factors and reduce the cancer burden through early detection of cancer. Prevention is the most important and effective long-term strategy for cancer control [32].

Cancer is a multistage process that involves mutational changes and uncontrolled cell proliferation. The etiology of cancer is linked to environmental and genetic inheritance causes. The physical (such as ultraviolet and ionizing radiation), chemical (such as asbestos, components of tobacco smoke, aflatoxin, and arsenic) and biological carcinogens (infections from certain viruses, bacteria, or parasites) may play a role in tumor genesis. The accumulation of molecular damage in DNA, proteins and lipids during the aging progress is also characterized by an increase in intracellular oxidative stress due to the progressive decrease of the intracellular ROS scavenging [33]. Therefore, oxidative stress and the resulting oxidative damage are important contributors to the formation and progression of cancer [34].

2.3 Bioactive components of *Salvia miltiorrhiza* (Danshen)

Salvia miltiorrhiza (Danshen) belongs to the *Lamiaceae* family. There are at least 49 diterpenoid quinones, more than 36 hydrophilic phenolic acids, and 23 essential oil constituents have been isolated and identified from Danshen [35]. Our previous population-based studies demonstrated that Danshen is the most common herbal drug used to treat ischemic heart disease [36] and ischemic stroke [37].

The predominant bioactive compounds in Danshen contains two major groups of chemicals [8, 38]. The first group includes lipophilic compounds (Terpenoids) such as tanshinone I, tanshinone IIA, acetyltanshinone IIA, cryptotanshinone, isocryptotanshinone, dihydrotanshinone, 15,16-dihydrotanshinone I, and miltirone (**Figure 1b**). These terpenoids possess a wide range of biological activities including antioxidant [39], antibacterial [40], anti-inflammatory [41], antiatherogenic, neuroprotective [42], antitumor [43, 44], and antidiabetic [39] effects.

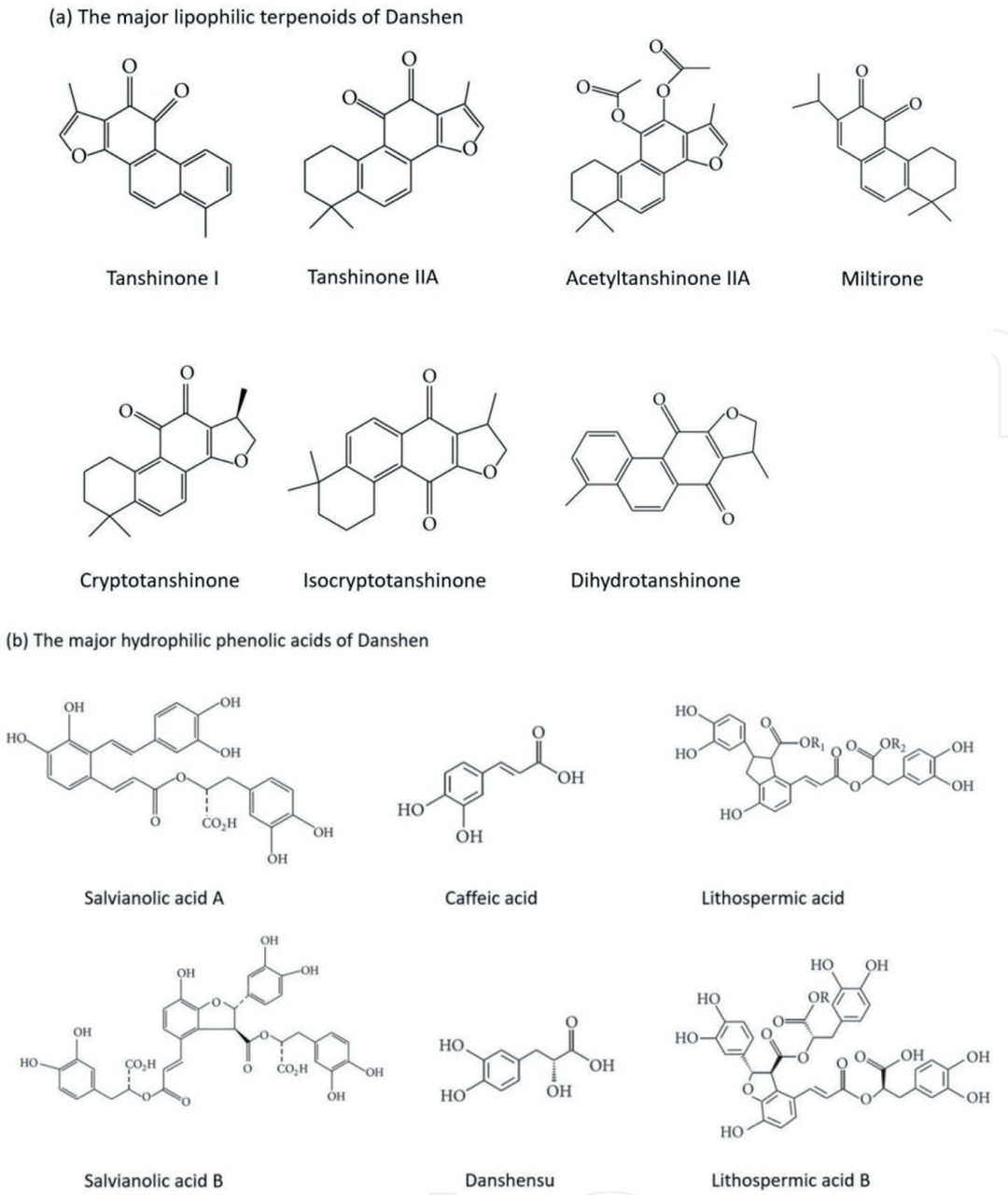

Figure 1.
The chemical structures of major (a) lipophilic terpenoids and (b) hydrophilic phenolic acids of Danshen.

The second group includes the hydrophilic phenolic acids such as caffeic acid, danshensu, salvianolic acid A(SalA), salvianolic acid B(SalB), lithospermic acid and lithospermic acid B (**Figure 1b**). Tanshinones show antibacterial, antioxidant, and antineoplastic activities, whereas phenolic acids possess more antioxidant and anticoagulant activities [45]. The classification of polyphenols mainly includes flavonoids (60%), phenolic acids (30%), and other polyphenols (including stilbenes and lignans) [46]. The main polyphenols in Danshen are phenolic acids (including SalA, SalB, rosmarinic acid, and their derivatives) and flavonoids, which exhibit anti-oxygenation, anti-ischemia–reperfusion injury, anti-thrombosis, anti-tumor, and other therapeutic effects [47]. The main polyphenolic compounds are based on caffeic acid (3,4-dihydroxycinnamic acid), one of the most common phenolic acids, formed from two to four or more caffeic acid units, is one of the most common phenolic acids, frequently exist in fruits, grains, as well as TCM [48].

3. Oxidative stress in aging-associated cardiovascular disease and cancer

3.1 Oxidative stress and aging-associated cardiovascular disease

Decreasing in absolute number of cardiomyocytes due to increased apoptosis and necrosis and decreasing in repopulation of cardiomyocytes from cardiac stem cell reserves were occurred in aging heart [49, 50]. The increase in oxidative stress due to the increase in ROS production with age results in an overall enhancement in the rate of cardiomyocyte death with age. With advancing age, we accumulate mutations in our somatic cells. The expression of such factors as p53, p21, p16, senescence-associated β-galactosidase activity and phosphorylation status of γ-H2Ax are widely used to detect the DNA damage. These biomarkers of aging can be used in cardiac tissue to assess how modulation of longevity genes influences the rate and degree of cardiovascular aging at the cellular level [51, 52].

Many aging-associated CVDs including ischemia/reperfusion, hypertensive heart disease and diabetes are related to oxidative stress and that will exhibit cytokines. In addition, increased ROS-responsive signaling pathways are objective by inflammatory oxidative stress and ROS generative system like unfolded protein response of the endoplasmic reticulum or NADPH oxidase activation [53].

The Apoptosis signal-regulating kinase 1(ASK1)-signalosome regulates p38 MAPK and SAPK/JNK and NFκB signaling networks promote senescence (in vitro) and aging (in vivo, animal models and human cohorts) in response to oxidative stress and inflammation leading to age-associated CVDs. Furthermore, their inhibition delays the onset of these CVDs as well as senescence and aging [53, 54].

The Energy generation from mitochondria is through oxidative phosphorylation and will also increase in ROS production which leads to free radical–imposed damage to macromolecules and cellular component. $p66^{Shc}$, a mitochondrial adaptor, plays an important role in the generation of ROS and as a molecular effector which may explain how aging is connected with CVD and metabolic disease [55]. Several studies show that increased $p66^{Shc}$ expression with time may promote ROS accumulation with subsequent deregulation of pathways implicated in mitochondrial dysfunction, fat accumulation, insulin resistance and diabetes [56–58].

The AMPK-SIRT1 pathway is involved in energy metabolism in cell. The functional AMP-activated protein kinase (AMPK) is a heterotrimer consisting of a catalytic alpha (α), a regulatory gamma (γ) and a scaffolding beta (β) subunit and is activated by low cellular energy status [59]. AMPK activates eNOS, and facilitates autophagy and mitophagy, thus preventing mitochondrial insufficiency, inflammation and cellular death [60]. Sirtuin 1 (SIRT1) is a NAD^+-dependent class III histone deacetylase (HDAC) that mediates the effects of caloric restriction on lifespan and metabolic pathways in various organisms. SIRT1 prevents cardiovascular aging by activating of eNOS [61].

3.2 Oxidative stress in cancer

Cancer is a multistage process defined by at least three stages: initiation, promotion, and progression [62]. ROS from both endogenous and exogenous sources result in increased oxidative stress in the cell. Oxidative stress modulates gene expression of downstream targets involved in DNA repair, cell proliferation and in part through activation or inhibition of transcription factors and second messengers. The role of single nuclear polymorphism for oxidative DNA repair and enzymatic antioxidants is important in determining the potential human cancer risk [34].

ROS regulates tumor development including following steps: transformation [63], survival [64], proliferation [65], invasion [66], metastasis [67], and angiogenesis [68]. One study showed the oxidative stress may be positive correlation with lung cancer staging [69]. In breast carcinomas, 8-OHdG (a most widely used fingerprint of radical attack towards DNA) might be increased 8- to 17-fold in breast primary tumors compared with non-malignant breast tissue [70].

H_2O_2 plays an important role in carcinogenesis because it is capable of diffusing throughout the mitochondria and across cell membranes and producing many types of cellular injury [71]. ROS may down-regulate the expression of the DNA mismatch repair genes (mutS homolog 2 and 6) and inhibit its enzymatic activity. ROS also induce the expression of DNA methyltransferases, leading to a total hypermethylation of the genome [72]. DNA methylation silence several tumor suppressor genes promoter, such as adenomatous polyposis coli (APC), cyclin-dependent kinase inhibitor-2 (CDKN-2), breast cancer susceptibility gene 1 (BRCA1), retinoblastoma protein (Rb), and the DNA mismatch repair gene, human mutL homolog 1 (hMLH1) [73, 74].

However, it is interesting that oxidative stress induces cancer, but also exists opposite condition. When ROS produced in large excess, they endanger the viability of the cancer cells, through the sustained activation of the cell cycle inhibitors [75]. To protect themselves from ROS-mediated toxicity, many types of cancers enhance the intrinsic antioxidant defenses, which make them dependent on the efficacy of a given ROS-detoxifying system. This poses an attractive target for anticancer therapy by using prooxidants or inhibiting of a chosen antioxidant system [76]. Whether ROS promote tumor cell survival or act as anti-tumorigenic agents depends on the cell and tissues, the location of ROS production, and the concentration of individual ROS.

4. Mechanisms of *Salvia miltiorrhiza* in aging-associated CVD and cancer

4.1 Therapeutic properties of Danshen in aging-associated CVD

Salvianolic acids, especially SalA and SalB, have potent anti-oxidative capabilities due to their polyphenolic structure. The cardiovascular protection of salvianolic acids include the following mechanisms: ROS scavengers, reduction of leukocyte-endothelial adherence, inhibition of inflammation and metalloproteinases expression from aortic smooth muscle cells, and indirect regulation of immune function, and also competitive binding to target proteins to interrupt protein–protein interactions [77].

SalA inhibits oxidative stress directly by scavenging the free radicals to improve the endothelial dysfunction [78], vascular smooth muscle cell proliferation [79], pulmonary arterial hypertension [80], and cardiac fibrosis. SalA can chelate Cu^{2+} and inhibit Cu^{2+}-promoted oxidation of low-density lipoprotein to reduce the production of malondialdehyde which is the final product of polyunsaturated fatty acids peroxidation in a cell-free system [81]. Interesting, there is a study showed both Salvianolic acid and tanshinone contribute to the cardioprotective effect of Danshen. Tanshinone mainly inhibits intracellular calcium and cell adhesion pathways at an early stage after ischemic injury whereas Salvianolic acid acts mainly by decreasing apoptosis [82].

SalB protects human endothelial progenitor cells against oxidative stress-mediated dysfunction by modulating Akt/mTOR/4EBP1, p38 MAPK/ATF2, and ERK1/2 signaling pathways and prevents oxidative-induced endothelial dysfunction via down-regulated NADPH oxidase 4 and eNOS expression [18].

Cardiac fibrosis is a chronic harmful result of hypertension which may further advance to heart failure and increased matrix metalloproteinase-9 (MMP-9) contributes to the underlying mechanism. In neonatal cardiac fibroblast, SalA inhibited fibroblast migration, blocked myofibroblast transformation, inhibited secretion of intercellular adhesion molecule (ICAM), interleukin-6 (IL-6) and soluble vascular cell adhesion molecule-1 (sVCAM-1) as well as collagen induced by MMP-9. The inhibition on MMP-9 by SalA was further confirmed in cultured cardiac H9c2 cell overexpressing MMP-9 in vitro and in heart of spontaneously hypertensive rats (SHR) in vivo [83]. SalA targeted transgelin and had a protective effect on myocardium by stabilizing the transgelin-actin complex, modulating the reorganization of the actin cytoskeleton, facilitating F-actin bundling, further enhancing the contractility and blood flows of coronary arteries, and improving outcomes of myocardial ischemia [84]. SalB facilitates angiogenesis and alleviated cardiac fibrosis and cardiac remodeling in diabetic cardiomyopathy by suppressing insulin-like growth factor-binding protein 3 (IGFBP3) [85]. SalB can alleviate Ang II-induced cardiac fibrosis via suppressing the NF-κB pathway in vitro [86]. It is reported that treatment with 5% water-soluble extract of Danshen which contained SalB for 12 weeks lowers blood cholesterol and reduces atherosclerotic plaque formation in diet-induced hypercholesterolemic rabbits, which is associated with its ROS scavenging capacity (**Table 1**) [87].

Homocysteine (Hcy), a by-product of methionine metabolism, may lead to hyperhomocysteinemia which is the risk factors responsible for the development of several vascular diseases (thromboembolism, atherosclerosis, stroke, vascular diseases and dementia). The aqueous extracts of Danshen against vascular atherosclerotic lesions though inhibiting Hcy-induced rat smooth muscle cell line(A10) growth via the PKC/MAPK-dependent pathway, attenuated carbonyl-modification of specific cytoskeleton and chaperone proteins leading to cell type transformation, also, scavenging of ROS and subsequent modulation of protein carbonylation to inhibit cell proliferation [88]. Another study demonstrated the protective effect of Danshen extract against the Hcy-induced adverse effect on human umbilical vein endothelial cell and showed different effectiveness in protection according to the following descending order: Danshen aqueous extract, 3-(3,4-dihydroxyphenyl)-2-hydroxy-propionic acid (Danshensu), protocatechuic acid, catechin and protocatechualdehyde [89]. Danshensu decreases foam cell formation by reducing the expression of TNFα, ICAM-1, and ET-1 while increasing NO production, thus protecting the vascular endothelium from injury [90]. SalA markedly attenuated induction of MKP-3(mitogen-activated protein kinase phosphatases 3) and inhibition of eNOS expression and NO formation under endothelial ischemia/reperfusion condition [91].

Some clinical studies reported that the Danshen preparations in combination with Western medicine were more effective for treatment of various CVDs including angina pectoris, myocardial infarction, hypertension, hyperlipidemia, and pulmonary heart diseases [92]. Our previous series studies showed the most common used single Chinese herbal products which prescribed by TCM Doctors during 2000–2010 in Taiwan is Danshen (16.50% in ischemic stroke; 29.30% in ischemic heart disease; 3.95% in atrill fibrillation; 5.13% in heart failure) [36, 37, 93, 94]. There was nearly one-third lower stroke risk in ischemic heart disease patients with combination TCM than patients with non-TCM treatment (95% CI = 0.11–0.84, P = .02). The higher survival rate (P < .001) and the lower incidence of hemorrhagic stroke (P = .04) in ischemic heart disease patients with TCM treatment was reported [95]. Compared to non-TCM users, the stroke risk was significantly lower in TCM users with atrial fibrillation who were female or younger than 65 years, but not in males, people more than 65 years old, or people with comorbidities [93].

Component	Pathology of CVD	Mechanism	References
Salvianolic acid A	Endothelial dysfunction	⊕ microvascular remodeling	[78]
	Vascular smooth muscle cell proliferation	⊕ p21 expression via cAMP/PKA/CREB signaling cascade	[79]
	Pulmonary arterial hypertension	↓ right ventricular systolic pressure ↓ hypertrophic damage of myocardium, parenchymal injury and collagen deposition in the lungs	[80]
	Lipid oxidation	chelate Cu^{2+} and ⊖ Cu^{2+}-mediated oxidation of LDL ↓ reducing MDA	[81]
	hypertension	⊖ MMP-9	[83]
	myocardial ischemia	stabilize the transgelin-actin complex modulate the reorganization of the actin cytoskeleton ⊕ F-actin bundling, ↑ contractility and blood flows of coronary arteries	[84]
Salvianolic acid b	Endothelial dysfunction	modulating Akt/mTOR/4EBP1, p38 MAPK/ATF2 ↑ ERK1/2 signaling pathways ↓ Nox4 and eNOS	[18]
	Atherosclerotic plaque formation	↓ LDL ⊖ atherosclerotic plaque formation ⊕ scavenging ROS	[87]
	Cardiac fibrosis	⊖ fibroblast migration and myofibroblast transformation ↓ ICAM, IL-6 and sVCAM-1 ⊖ MMP-9 ⊖ NF-κB pathway	[86]
	Diabetic cardiomyopathy	⊕ angiogenesis and cardiac remodeling ↓ cardiac fibrosis ⊖ IGFBP3	[85]

↑: increase; ↓: decrease; ↔: no change; ⊖: inhibit; ⊕: promote. cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; CREB, cAMP-response element binding protein; LDL, low-density lipoprotein; MDA, malondialdehyde; MMP-9, Matrix metallopeptidase 9; Akt, protein kinase B; mTOR, mechanistic target of rapamycin; 4EBP1, Eukaryotic translation initiation factor 4E-binding protein 1; p38 MAPK, mitogen-activated protein kinases; ATF2, Activating Transcription Factor 2; ERK1, extracellular signal-regulated kinase 1; Nox4, NADPH oxidase 4; eNOS, Endothelial Nitric Oxide Synthase; ROS, reactive oxygen species; ICAM, intercellular adhesion molecule; IL-6, interleukin-6; sVCAM-1, soluble vascular cell adhesion molecule-1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IGFBP3, insulin-like growth factor-binding protein 3.

Table 1.
The main antioxidative mechanisms of Salvia miltiorrhiza *(Danshen) in CVD.*

One randomized controlled trial showed *Salvia Miltiorrhiza* Depside Salt combined with aspirin is a clinically effective and safe intervention to treat adults aged 35 and older with stable angina pectoris without adverse drug reactions such as bleeding tendency occurred [96].

4.2 Therapeutic properties of Danshen in cancer

SalA and SalB have been reported to owe anti-cancer, anti-inflammatory and cardioprotective activities not only through inducing apoptosis, halting cell cycle

and adjourning metastasis by targeting multiple deregulated signaling networks of cancer but also sensitizing cancer cells to chemo-drugs [97].

Acting to protect the organism against these harmful pro-oxidants is a complex system of enzymatic antioxidants (e.g., superoxide dismutase (SOD), glutathione peroxidase, glutathione reductase, catalase) and nonenzymatic antioxidants (e.g., glutathione, vitamins C and D) [98].

SalA elevated ROS levels, downregulated P-glycoprotein, and triggered apoptosis by increasing caspase-3 activity and upregulating Bax expression, while downregulating Bcl-2 expression and disrupting the mitochondrial membrane potential in multidrug resistance MCF-7 human breast cancer cells [99]. In lung cancer, SalA could increase the chemotherapeutic efficacy of cisplatin by enhanced sensitivity to cisplatin in A549/DDP cells mainly through suppression of the c-met/AKT/mTOR signaling pathway [100]. In addition, SalA considerably suppressed the migrative and invasive activity of human NPC cells but not presented cytotoxicity. In SalA-treated NPC cells, the activity and expression of matrix metalloproteinase-2 (MMP-2), a key regulator of cancer cell invasion, were reduced. Additionally, the presence of high concentrations of SalA dramatically abolished the activation of focal adhesion kinase (FAK) and moderately inhibited the phosphorylation of Src and ERK in NPC cells [101].

The anti-tumor effect of SalB is via inhibiting the expression of glucosylceramide and GM3 synthases, and then increases the ceramide accumulation and ceramide-mediated Triple-negative breast cancer cell apoptosis. [102]. One study indicated SalB induced cell death and triggered autophagy in HCT116 and HT29 cells in a dose-dependent manner, and it is as a novel autophagy inducer in colorectal cancer cells through the suppression of AKT/mTOR pathway [103]. Besides,

Component	Cancer	Mechanism	References
Salvianolic acid A	Non-small cell lung cancer	↑ efficacy of DDP ⊖c-met/AKT/mTOR signaling pathway	[100]
	Breast cancer	↑ ROS in resistant cells ↑ apoptosis via caspase-3 activity, disrupted mitochondrial membrane potential, ↓ Bcl-2 and ↑ Bax in the resistant cells ↓ P-glycoprotein	[99]
	Nasopharyngeal carcinoma	↓ MMP-2 ⊖ FAK, Src, and ERK pathways	[101]
Salvianolic acid B	Colorectal cancer	⊕ cancer cell death and autophagy ⊖ AKT/mTOR pathway	[103]
	Head and neck carcinoma	⊖ COX-2/PGE-2 pathway ⊕ the promotion of apoptosis ⊕ angiogenesis.	[109]
	Hepatocellular cancer	↓ cytotoxicity of doxorubicin ↓ ROS by enhancing the expression of SOD and decreasing NADPH oxidase	[104]
	Gastric cancer	↓ the resistance to DDP via AKT/mTOR pathway	[105]

↑: increase; ↓: decrease; ↔: no change; ⊖: inhibit; ⊕: promote. ROS, reactive oxygen species; DDP, cisplatin; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein; FAK, focal Adhesion Kinase; ERK, extracellular signal regulated kinase; COX-2/PGE-2; SOD; NADPH.

Table 2.
The therapeutic effect mechanism of polyphenols of Salvia miltiorrhiza (Danshen) in common cancers.

SalB reduced the cytotoxicity of doxorubicin through scavenging ROS generated by doxorubicin in HepG2 cells and enhance the expression of SOD and decrease that of NADPH oxidase, which resulted in the elimination of ROS [104]. Sal-B regulated proliferation, epithelial-mesenchymal transition (EMT) and apoptosis to reduce the resistance to cisplatin via AKT/mTOR pathway in cisplatin-resistant gastric cancer cells [105].

Rosmarinic acid (RA) inhibited non-small cell lung cancer (NSCLC) by inducing G1 phase cell cycle arrest, apoptosis and the sensitivity of cisplatin-resistant cell via activating MAPK, enhancing p21 and p53 expression, and inhibiting the expression of P-gp and MDR1 [106]. RA reverses cisplatin resistance of NSCLS by activating the MAPK signaling pathway.

Most of the currently available chemotherapeutic and radiotherapeutic agents kill cancer cells by increasing ROS stress. Thus, both ROS-elevating and ROS-eliminating strategies have been developed for cancer therapy. As we know either chemotherapy or radiotherapy was usually associate with uncomfortable side-effects which are burdens to clinical physicians. Our previous researches find the aqueous extract of Danshen has shown anticancer as well as antioxidant effects, besides, it could prevent or mitigate the causative cardiomyopathy through controlling multiple targets without compromising the efficacy of chemotherapy (**Table 2**) [107, 108].

5. Conclusion

The current epidemiologic data show the incremental trend of CVD and cancer prevalence, mortality as well as disease burden expected in the next 40 years. The prevention of disease becomes the main lesson from now on to the future. Danshen plays a role as anti-oxidative agent and its therapeutic effects in diseases including age-associated CVDs and cancer are confirmed in many studies. Traditional Chinese medicine might be an option for treatment.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

CVD	Cardiovascular disease
ROS	Reactive oxygen species
TCM	Traditional Chinese medicine
LV	Left ventricular
eNOS	Endothelial nitric oxide synthetase
NO	Nitric oxide
SalA	Salvianolic acid A
SalB	Salvianolic acid B
AMPK	AMP-activated protein kinase
SIRT1	Sirtuin 1
MMP-9	Matrix metalloproteinase-9
Hcy	Homocysteine
SOD	Superoxide dismutase
RA	Rosmarinic acid
NSCLC	Non-small cell lung cancer

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